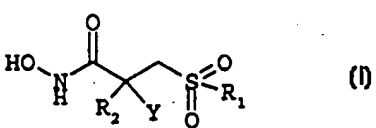




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> C07C 317/44, 317/46, 317/48, A61K 31/19	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/26909</b>  <b>(43) International Publication Date:</b> 3 June 1999 (03.06.99)
<b>(21) International Application Number:</b> PCT/IB98/02154  <b>(22) International Filing Date:</b> 18 November 1998 (18.11.98)  <b>(30) Priority Data:</b> 60/072,655 21 November 1997 (21.11.97) US  <b>(71) Applicant (for all designated States except US):</b> PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> WARPEHOSKI, Martha, A. [US/US]; 7600 Currylane, Portage, MI 49024 (US). MITCHELL, Mark, Allen [US/US]; 1628 Dover Road, Kalamazoo, MI 49008 (US). HARPER, Donald, E. [US/US]; 11520 Channel Drive, Plainwell, MI 49080 (US). MAGGIORA, Linda, Louise [US/US]; 4400 Glenrose Terrace, Kalamazoo, MI 49008 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 26 August 1999 (26.08.99)
<b>(54) Title:</b> ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS  <div style="text-align: center;">  </div> <b>(57) Abstract</b>  <p>The present invention provides a compound of formula (I), or pharmaceutical acceptable salts thereof wherein R<sub>1</sub> is C<sub>4-12</sub> alkyl, C<sub>4-12</sub> alkenyl, C<sub>4-12</sub> alkynyl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-8</sub> cycloalkyl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-aryl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-het, R<sub>2</sub> is substituted and unsubstituted C<sub>1-12</sub> alkyl, substituted and unsubstituted C<sub>2-12</sub> alkenyl, substituted and unsubstituted C<sub>2-12</sub> alkynyl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-8</sub> cycloalkyl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-8</sub> cycloalkenyl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-aryl, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-heterocyclic ring, substituted and unsubstituted -(CH<sub>2</sub>)<sub>n</sub>-X-R<sub>4</sub> (X is -O-, -S(=O)<sub>2</sub>-, -NR<sub>7</sub>-, -S(=O)<sub>2</sub>NR<sub>8</sub>-, or -C(=O)-), and -(CH<sub>2</sub>)<sub>n</sub>CHR<sub>5</sub>R<sub>6</sub>. The compounds are inhibitors of matrix metalloproteinases involved in tissue degradation.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
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CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 November 1999 (05.11.99)	
International application No. PCT/IB98/02154	Applicant's or agent's file reference 6146
International filing date (day/month/year) 18 November 1998 (18.11.98)	Priority date (day/month/year) 21 November 1997 (21.11.97)
Applicant WARPEHOSKI, Martha, A. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
18 June 1999 (18.06.99)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Marc Salzman Telephone No.: (41-22) 338.83.38
---	--

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BEAUMONT, William, E.  
Oblon, Spivak, McClelland, Maier &  
Neustadt, P.C.  
Suite 400  
1755 Jefferson Davis Highway  
Arlington, VA 22202  
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)

07 July 1999 (07.07.99)

Applicant's or agent's file reference

6146

## IMPORTANT NOTIFICATION

International application No.

PCT/IB98/02154

International filing date (day/month/year)

18 November 1998 (18.11.98)

## 1. The following indications appeared on record concerning:

☐

the applicant

☐

the inventor

☒

the agent

☐

the common representative

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☒

the name

☒

the address

☐

the nationality

☐

the residence

Name and Address

State of Nationality

State of Residence

BEAUMONT, William, E.  
Oblon, Spivak, McClelland, Maier &  
Neustadt, P.C.  
Suite 400  
1755 Jefferson Davis Highway  
Arlington, VA 22202  
United States of America

Telephone No.

703-413-3000

Facsimile No.

703-413-2220

Teleprinter No.

## 3. Further observations, if necessary:

**An agent has been appointed.**

## 4. A copy of this notification has been sent to:

☒

the receiving Office

☒

the designated Offices concerned

☐

the International Searching Authority

☐

the elected Offices concerned

☐

the International Preliminary Examining Authority

☐

other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

MAZZINI, Giuseppe  
Pharmacia & Upjohn S.p.A.  
V. le Pasteur, 10  
I-20014 Nerviano  
ITALIE

Date of mailing (day/month/year) 23 March 1999 (23.03.99)	
Applicant's or agent's file reference 6146	IMPORTANT NOTIFICATION
International application No. PCT/IB98/02154	International filing date (day/month/year) 18 November 1998 (18.11.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 21 November 1997 (21.11.97)
Applicant PHARMACIA & UPJOHN COMPANY et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
21 Nov 1997 (21.11.97)	60/072,655	US	11 Marc 1999 (11.03.99)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Ting Zhao



Telephone No. (41-22) 338.83.38

RECEIVED

FEB 2 1999

OBLON, SPIVAK, McCLELLAND, MAIER &amp; NEUSTADT, P.C.

PCT

Chem

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BEAUMONT, William E.  
OBLON, SPIVAK, McCLELLAND, MAIER &  
NEUSTADT, P.C.  
1755 Jefferson Davis Highway  
Fourth Floor  
Arlington, Virginia 22202  
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year) 21.02.2000

Applicant's or agent's file reference  
076904200XWO

## IMPORTANT NOTIFICATION

International application No.  
PCT/IB98/02154

International filing date (day/month/year)  
18/11/1998

Priority date (day/month/year)  
21/11/1997

Applicant  
PHARMACIA & UPJOHN COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

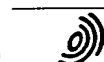
## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Pfützner, G

Tel. +49 89 2399-2879



DOCKET NO. 0769-0420-0X PCT

09/530965  
422 Rec'd PCT/PTO 18 MAY 2000

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

IN RE APPLICATION OF: Martha WARPEHOSKI, et al.

SERIAL NUMBER: NEW U.S. PCT APPLICATION (based on PCT/IB98/02154)

FILED: HEREWITH

FOR: ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS

**REQUEST FOR CONSIDERATION OF DOCUMENTS  
CITED IN INTERNATIONAL SEARCH REPORT**

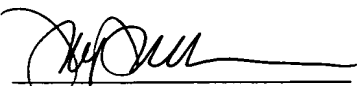
Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that applicant(s) request that the Examiner consider the documents cited in the International Search Report according to MPEP §609 and so indicate by a statement in the first Office Action that the information has been considered. When the Form PCT/DO/EO/903 indicates both the search report and copies of the documents are present in the national stage file, there is no requirement for the applicant(s) to submit them (1156 O.G. 91 November 23, 1993).

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, P.C.



William E. Beaumont  
Attorney of Record  
Registration No. 30,996

Fourth Floor  
1755 Jefferson Davis Highway  
Arlington, Virginia 22202  
(703) 413-3000  
Fax No. (703) 413-2220  
(OSMMN 1/97)

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>6146</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/IB 98/02154</b>	International filing date (day/month/year) <b>18/11/1998</b>	(Earliest) Priority Date (day/month/year) <b>21/11/1997</b>
Applicant <b>PHARMACIA &amp; UPJOHN COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**ALPHA-HYDROXY, -AMINO AND -FLUORO DERIVATIVES OF BETA-SULPHONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ Non of the figures.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 98/02154

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C317/44 C07C317/46 C07C317/48 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 780 386 A (HOFFMANN LA ROCHE ; AGOURON PHARMA (US)) 25 June 1997 cited in the application see the whole document ---	1
A,P	WO 98 13340 A (WARPEHOSKI MARTHA A ; UPJOHN CO (US); HARPER DONALD E (US)) 2 April 1998 cited in the application see the whole document ---	1
P,X	WO 98 39326 A (MCDONALD JOSEPH J ; BOEHM TERRI L (US); MONSANTO CO (US); FRESKOS J) 11 September 1998 see the whole document --- -/--	1-3,5,6, 15-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 June 1999

Date of mailing of the international search report

25/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Goetz, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 98/02154

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 119, no. 23, 6 December 1993 Columbus, Ohio, US; abstract no. 240883, BOYLE, G. W. ET AL: "Metabolism of Casodex in laboratory animals" XP002105163 see RN: 151262-57-6 see abstract & XENOBIOTICA (1993), 23(7), 781-98 CODEN: XENOBH; ISSN: 0049-8254, ---	4
X	CHEMICAL ABSTRACTS, vol. 108, no. 17, 25 April 1988 Columbus, Ohio, US; abstract no. 150945, GRIFFITH, OWEN W.: "Amino acid sulfones: S-benzyl-DL-.alpha.-methylcysteine sulfone" XP002105164 see RN: 113737-61-4 see abstract & METHODS ENZYMOL. (1987), 143(SULFUR SULFUR AMINO ACIDS), 274-9 CODEN: MENZAU; ISSN: 0076-6879, -----	4

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 98/02154


Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0780386 A	25-06-1997	AU 700725 B	14-01-1999
		AU 7548296 A	31-07-1997
		BR 9606134 A	03-11-1998
		CA 2193178 A	21-06-1997
		CN 1160045 A	24-09-1997
		CZ 9603740 A	14-01-1998
		HR 960612 A	28-02-1998
		HU 9603494 A	30-11-1998
		JP 9249638 A	22-09-1997
		NO 965413 A	23-06-1997
		NZ 299941 A	27-05-1998
		PL 317604 A	23-06-1997
WO 9813340 A	02-04-1998	AU 4645997 A	17-04-1998
WO 9839326 A	11-09-1998	AU 6447898 A	22-09-1998
		AU 6542498 A	22-09-1998
		AU 6686598 A	22-09-1998
		WO 9839315 A	11-09-1998
		WO 9839316 A	11-09-1998
		WO 9838859 A	11-09-1998

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>076904200XWO</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/IB98/02154</b>	International filing date (day/month/year) <b>18/11/1998</b>	Priority date (day/month/year) <b>21/11/1997</b>
International Patent Classification (IPC) or national classification and IPC <b>C07C317/44</b>		
Applicant <b>PHARMACIA &amp; UPJOHN COMPANY et al.</b>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II   <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV   <input type="checkbox"/> Lack of unity of invention</li> <li>V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI   <input checked="" type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul>		
Date of submission of the demand  <b>18/06/1999</b>	Date of completion of this report  <b>21.02.2000</b>	
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  <b>Goetz, G</b>  Telephone No. +49 89 2399 8105	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IB98/02154

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-34 as originally filed

**Claims, No.:**

1-19 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 7-14.

because:

- ☒ the said international application, or the said claims Nos. 7-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IB98/02154

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-3,5-19
	No:	Claims	4
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,15-19
	No:	Claims	

**2. Citations and explanations**

see separate sheet

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IB98/02154

**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 7-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 7-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: Chem. Abs. 119: 240883 (06-12-1993),

D2: Chem. Abs. 108: 150945 (25-04-1988),

The documents D1 (RN:151262-57-6) and D2 (RN:113737-61-4) disclose compounds falling within the scope of formula 8 of claim 4

D3: EP-A-0780386

The following statement is made with the proviso that the compounds of D1 and D2 are disclaimed from the subject matter of claim 4.

The claimed compounds differ from the prior art compounds as disclosed in D3 in that the carbon atom in alpha-position to the hydroxamic group must be substituted with either a hydroxy- or amino-group or a fluorine atom and simultaneously in beta-position must be a CH<sub>2</sub>-group.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IB98/02154

Such a selection of substituents is not disclosed in the prior art.  
Present claims 1 to 3,5,6 (active compounds), 4 (intermediate), 7-19 (pharm. composition, first and second medical use) relate thus to novel subject matter (Article 33.2 PCT).

These structural features and from the prior art delimiting features are not rendered obvious from the available prior art. In particular it was not obvious that the resulting compounds have an inhibitory activity to matrix metalloproteinases. Claims 1-19 are thus considered to meet the inventive step requirement (Article 33.3 PCT).

3. The industrial applicability is acknowledged for all examined claims (Article 33.4 PCT).

**Re Item VI**

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-98/39326	11.09.98	04.03.98	04.03.97

This document discloses alpha-hydroxy-beta-sulfonyl-hydroxamic acids which are novelty-destroying for those compounds of the present application where Y is hydroxy.



# INTERNATIONAL SEARCH REPORT

Inter: nat Application No

PCT/IB 98/02154

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C317/44 C07C317/46 C07C317/48 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 780 386 A (HOFFMANN LA ROCHE ; AGOURON PHARMA (US)) 25 June 1997 cited in the application see the whole document ---	1
A,P	WO 98 13340 A (WARPEHOSKI MARTHA A ; UPJOHN CO (US); HARPER DONALD E (US)) 2 April 1998 cited in the application see the whole document ---	1
P,X	WO 98 39326 A (MCDONALD JOSEPH J ; BOEHM TERRI L (US); MONSANTO CO (US); FRESKOS J) 11 September 1998 see the whole document --- -/--	1-3, 5, 6, 15-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 June 1999

Date of mailing of the international search report

25/06/1999

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Goetz, G

# INTERNATIONAL SEARCH REPORT

Inter national Application No  
PCT/IB 98/02154

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 119, no. 23, 6 December 1993 Columbus, Ohio, US; abstract no. 240883. BOYLE, G. W. ET AL: "Metabolism of Casodex in laboratory animals" XP002105163 see RN: 151262-57-6 see abstract & XENOBIOTICA (1993), 23(7), 781-98 CODEN: XENOBH;ISSN: 0049-8254, ---	4
X	CHEMICAL ABSTRACTS, vol. 108, no. 17, 25 April 1988 Columbus, Ohio, US; abstract no. 150945, GRIFFITH, OWEN W.: "Amino acid sulfones: S-benzyl-DL-.alpha.-methylcysteine sulfone" XP002105164 see RN: 113737-61-4 see abstract & METHODS ENZYMOL. (1987), 143(SULFUR SULFUR AMINO ACIDS), 274-9 CODEN: MENZAU;ISSN: 0076-6879, -----	4

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 98/02154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0780386 A	25-06-1997	AU 700725 B	14-01-1999
		AU 7548296 A	31-07-1997
		BR 9606134 A	03-11-1998
		CA 2193178 A	21-06-1997
		CN 1160045 A	24-09-1997
		CZ 9603740 A	14-01-1998
		HR 960612 A	28-02-1998
		HU 9603494 A	30-11-1998
		JP 9249638 A	22-09-1997
		NO 965413 A	23-06-1997
		NZ 299941 A	27-05-1998
		PL 317604 A	23-06-1997
WO 9813340 A	02-04-1998	AU 4645997 A	17-04-1998
WO 9839326 A	11-09-1998	AU 6447898 A	22-09-1998
		AU 6542498 A	22-09-1998
		AU 6686598 A	22-09-1998
		WO 9839315 A	11-09-1998
		WO 9839316 A	11-09-1998
		WO 9838859 A	11-09-1998

PATENT COOPERATION TREATY

PCT

REC'D 23 FEB 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 076904200XWO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB98/02154	International filing date (day/month/year) 18/11/1998	Priority date (day/month/year) 21/11/1997
International Patent Classification (IPC) or national classification and IPC C07C317/44		
Applicant PHARMACIA & UPJOHN COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  18/06/1999	Date of completion of this report  21.02.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4455	Authorized officer  Goetz, G  Telephone No. +49 89 2399 5105



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/02154

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-34 as originally filed

### Claims, No.:

1-19 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 7-14.

because:

- ☒ the said international application, or the said claims Nos. 7-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB98/02154

**s    separat   sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  
- ☐ no international search report has been established for the said claims Nos. .

## **V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

### **1. Statement**

Novelty (N)	Yes:	Claims	1-3,5-19
	No:	Claims	4
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,15-19
	No:	Claims	

### **2. Citations and explanations**

**see separate sheet**

## **VI. Certain documents cited**

### **1. Certain published documents (Rule 70.10)**

and / or

### **2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 7-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 7-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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D2: Chem. Abs. 108: 150945 (25-04-1988),

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D3: EP-A-0780386

The following statement is made with the proviso that the compounds of D1 and D2 are disclaimed from the subject matter of claim 4.

The claimed compounds differ from the prior art compounds as disclosed in D3 in that the carbon atom in alpha-position to the hydroxamic group must be substituted with either a hydroxy- or amino-group or a fluorine atom and simultaneously in beta-position must be a CH<sub>2</sub>-group. ✓

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IB98/02154

Such a selection of substituents is not disclosed in the prior art.  
Present claims 1 to 3,5,6 (active compounds), 4 (intermediate), 7-19 (pharm. composition, first and second medical use) relate thus to novel subject matter (Article 33.2 PCT).

These structural features and from the prior art delimiting features are not rendered obvious from the available prior art. In particular it was not obvious that the resulting compounds have an inhibitory activity to matrix metalloproteinases. Claims 1-19 are thus considered to meet the inventive step requirement (Article 33.3 PCT).

3. The industrial applicability is acknowledged for all examined claims (Article 33.4 PCT).

**Re Item VI**

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-98/39326	11.09.98	04.03.98	04.03.97

This document discloses alpha-hydroxy-beta-sulfonyl-hydroxamic acids which are novelty-destroying for those compounds of the present application where Y is hydroxy.